University of Thessaly

Faculty of Medicine

Master in Research Methodology in Biomedicine, Biostatistics and Clinical Bioinformatics at the University of Thessaly

''Assessement of the reporting quality of randomized controlled trials in the treatment of multiple sclerosis with Natalizumab, based on Consort statement.''

''Αξιολόγηση της ποιότητας αναφοράς των τυχαιοποιημένων ελεγχόμενων δοκιμών για τη θεραπεία της σκλήρυνσης κατά πλάκας με Ναταλιζουμάμη, βασισμένη στη δήλωση Consort.''

ΚΟΜΑΤΣΙΟΥΛΗ ΒΑΣΙΛΙΚΗ - ΦΑΡΜΑΚΟΠΟΙΟΣ

Τριμελής Συμβουλευτική Επιτροπή

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A) SUMMARY

a. Introduction

The treatment of multiple sclerosis has witnessed major progress since the first effective disease modifying treatment, ß-interferon, became available in 1993. One of the most remarkable new treatments has been natalizumab. Proper reporting of randomized controlled trials for this is necessary for the assessment of their validity.

b. Purpose

The aim of this study was to examine the reporting quality of randomized controlled trials (RCTs), concerning the use of Natalizumab from patients with multiple sclerosis.

c. Methods

PubMed was searched for English-language RCTs involving patients with multiple sclerosis (MS). Trials were considered eligible when participants were randomly assigned to at least two medicinal treatment arms. Quality of reporting was assessed using a 39–item questionnaire based on the CONSORT checklist.

d. Results

Finally, 7 RCTs were deemed eligible to be included in the present study and the overall compliance for them was 57,8% of applicable items. 9 of the 38 items of the checklist were addressed in 75% or more of the studies and only 1 item reached a successful reporting proportion of 100%.

e. Conclusion

Completeness of reporting in RCTs focusing on patients with MS using Natalizumab still remains unsatisfactory. These results suggest that further actions should be taken by authors, reviewers, and editors, since inadequate reporting makes the interpretation of RCTs difficult if not impossible.

Abbreviations and Acronyms

RCT = randomized controlled trial

CONSORT = Consolidated Standards of Reporting Trials

MS = Multiple Sclerosis

Α ΠΕΡΙΛΗΨΗ

a. Εισαγωγή

Η θεραπεία της σκλήρυνσης κατά πλάκας δεν είχε ιδιαίτερη πρόοδο έως την πρώτη αποτελεσματική θεραπεία , την β-ιντερφερόνη, που δώθηκε σε διαθεσιμότητα το 1993. Μία από τις αξιοσημείωτες θεραπείες αυτής της νόσου είναι η ναταλιζουμάμπη. Σωστή αναφορά τυχαιοποιημένων ελεγχόμενων δοκιμών γι αυτήν είναι απαραίτητη για την αξιολόγηση της εγκυρότητάς της.

b. Στόχοι

Στόχος αυτής της μελέτης ήταν να εξετάσει την ποιότητα αναφοράς των τυχαιοποιημένων ελεγχόμενων δοκιμών που αφορούν τη χρήση της ναταλιζουμάμπης από ασθενείς με σκλήρυνση κατά πλάκας.

c. Μέθοδοι

Πραγματοποιήθηκε αναζήτηση στο PubMed για RCTs στην αγγλική γλώσσα και με ασθενείς με MS. Δοκιμές που κρίθηκαν κατάλληλες για επιλογή περιείχαν συμμετέχοντες που τυχαιοποιήθηκαν σε τουλάχιστον δυο γκρουπ ιατρικής θεραπείας. Η ποιότητα αυτής της αναφοράς αξιολογήθηκε χρησιμοποιώντας μια λίστα 39 ερωτήσεων βασισμένη στη λίστα Consort.

d. Αποτελέσματα

Εν τέλει, 7 RCTs κρίθηκαν κατάλληλα για επιλογή για να συμπεριληφθούν σε αυτήν την έρευνα και η συνολική συμμόρφωση τους με την Consort ήταν 57,8%. 9 στα 38 ερωτήματα της λίστας απαντήθηκαν θετικά σε ποσοστό μεγαλύτερο του 75% και μόνο 1 ερώτημα απαντήθηκε θετικά κατά 100%.

e. Συμπέρασμα

Η ολοκλήρωση της αναφοράς των RCTs για ασθενείς με σκλήρυνση κατά πλάκας που χρησιμοποιούν ναταλιζουμάμπη, ακόμη παραμένει ανικανοποίητη. Αυτά τα αποτελέσματα προτείνουν σε συγγραφείς, κριτικούς και εκδότες να λάβουν περαιτέρω δράσεις, εφόσον η ανεπαρκής αναφορά καθιστά την ερμηνεία των RCTs δύσκολή, αν όχι αδύνατη.

B) INTRODUCTION

MS and Natalizumab

Multiple sclerosis (MS) is an autoimmune condition that results in inflammatory damage to the central nervous system (CNS). The pathologic hallmarks of MS are diffuse and focal areas of inflammation, demyelination, gliosis, and neuronal injury in the optic nerves, brain, and spinal cord. In addition to affecting white matter tracts, MS results in injury to the cortical and deep gray matter. The neurologic symptoms and disability that patients with MS experience are a direct consequence of these pathologic processes, resulting in acute and chronic disruption of white matter tracts and gray matter structures.

MS is the most common nontraumatic cause of neurologic disability in persons younger than 40 years, with an estimated prevalence of 400 000 in the United States. It occurs in a female–male ratio of 3 to 1. The cause of MS is multifactorial and is probably the cumulative result of multiple genetic and environmental risk factors. Twin studies have shown concordance rates between 20% and 30% in monozygotic twins and between 2% and 3% in dizygotic twins. Genome-wide assays have identified risk alleles in genes for major histocompatibility complex, interleukin-2 receptor, and interleukin-7 receptor, among others. Geographic location of residence before adolescence is also predictive of MS risk, with increased rates of the disease in northern and southern latitudes compared with equatorial countries. Reduced sunlight exposure in these regions may explain some of this distribution. Because ultraviolet radiation to the skin is the major source of vitamin D synthesis, living in regions with low levels of seasonal sunlight is associated with an increased risk for MS in individuals with vitamin D deficiency. Risk may also be influenced by exposure or lack of exposure to particular infectious agents because antibodies against certain viruses (such as Epstein–Barr virus) are more frequently seen in patients with MS than in those without it.

After more than 20 years using interferons and glatiramer acetate, an evolutionary improvement of patients treated with these drugs, as well as a better knowledge of its adverse effects and therapeutic response were observed.

Despite the proven efficacy of the immunomodulatory drugs, some patients (from 3 to 50%) did not respond well to treatment, showing an unsatisfactory evolution, with increased number of outbreaks, increased brain lesion load, and progressive disability.

Monoclonal antibodies have emerged as a therapeutic option for the treatment of multiple sclerosis. Natalizumabe (NTZ) is a humanized monoclonal antibody that binds to integrin **α**4B1, with a relevant immunomodulatory effect.

RCTs and Consort

The highest rank within the clinical studies is occupied by the randomized controlled trials (RCT) which consider to be ‘‘the most powerful tool in modern clinical research’’.

Readers need to know the quality of the trials, in order to assess the strengths and limitations of RCTs. In addition, healthcare providers depend upon the reporting of methodological factors in the reports of RCTs to allow them to determine the validity of the trials upon which they base their clinical practice and their treatment guidelines.

The evaluation of the methodological quality of a trial is connected with the quality of the reporting of its design, conduct and analysis. Over the years, scales and checklists have been developed in order to appraise the quality of RCT reports.

The CONSORT (Consolidated Standards of Reporting Trials) statement is a set of recommendations (first published in 1996 and revised twice, in 2001 and 2010) aiming at helping authors improve the reporting of randomized clinical trials. It includes a list of necessary elements that the authors should include in their trials report, thus ensuring its integrity and transparency. Since its first publication, the CONSORT statement has been endorsed by a multitude of scientific journals and prominent institutions. A number of studies have examined the effect the adoption of the CONSORT statement has had on the quality of RCT reporting. Hopewell et al. compared the reporting quality for RCTs published before and after the 2001 CONSORT revision and found it to be improved. Plint et al. compared the reporting quality of RCTs between journals endorsing and those not endorsing the CONSORT principles. For CONSORT adopters they also compared publications before and after their endorsement of CONSORT. They concluded that the adoption of the CONSORT statement had a beneficial impact on the reporting quality of RCTs. A Cochrane review by Turner et al. also concluded that journal adoption of the CONSORT statement improved the completeness of RCT reporting. Although the primary goal of the CONSORT statement is to guide authors to properly report RCTs, it has also been used as a tool for the assessment of the reporting quality of already published RCTs. Many studies have used the CONSORT principles in order to evaluate the overall reporting quality of RCTs in medical fields such as endocrinology, hematology, dermatology, pediatrics, otolaryngology and surgery. Few such studies have been conducted in the field of neurology.

C) METHODS

Search plan and RCT selection

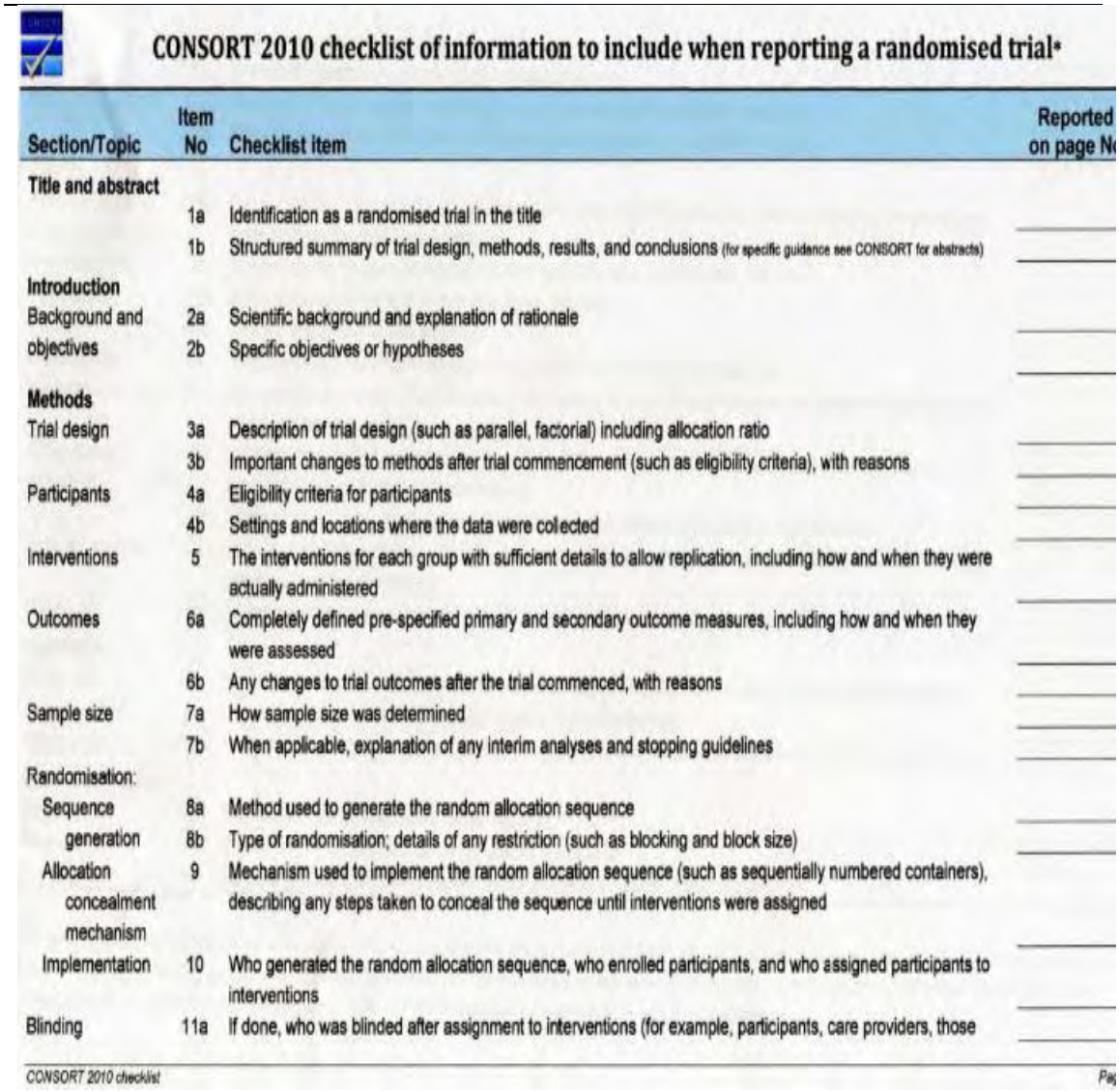
In order to identify the randomized controlled trials to be included in the present study, a computerized search in Pubmed was conducted in August 2017. The search terms used were ''multiple sclerosis'' annatalizumab''. The filters applied were ''Randomised controlled trials'' for the article type, ''Humans'' for species and ''English'' language. Search results were first screened for eligibility by title, then by abstract and finally by full text review when deemed necessary.

Eligibility of Studies

Trials were eligible if they had randomly assigned participants to at least two medicinal treatment arms and included patients with MS, using Natalizumab including all different types of the disease (Relapsing Remitting MS, Primary Progressive MS, Secondary Progressive MS, Clinically Isolated Syndrome and first demyelinating event suggestive of MS). Reports of trials on MS symptoms treatments, non-medicinal treatments, dose comparison studies, small pilot studies and any article with information resulting from a previous conducted trial (post-hoc analysis, sub-group analysis, sub-studies) where excluded.

Data Extraction and Reporting Assessment Tool

As assessment tool for quality of reporting of randomized controlled trials (RCTs), we used the CONSORT checklist, revised in 2010, which includes a 25-item checklist (Pictures 1 and 2) and a flow diagram (Figure 1). The checklist provides standardized approaches to report the trial design, analysis, and interpretation, and the diagram gives instructions to display the progress of all participants throughout the trial.



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	

CONSORT 2010 checklist

Picture 1. CONSORT 2010 checklist

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

CONSORT 2010 checklist

Page

Picture 2. CONSORT 2010 checklist (continued)

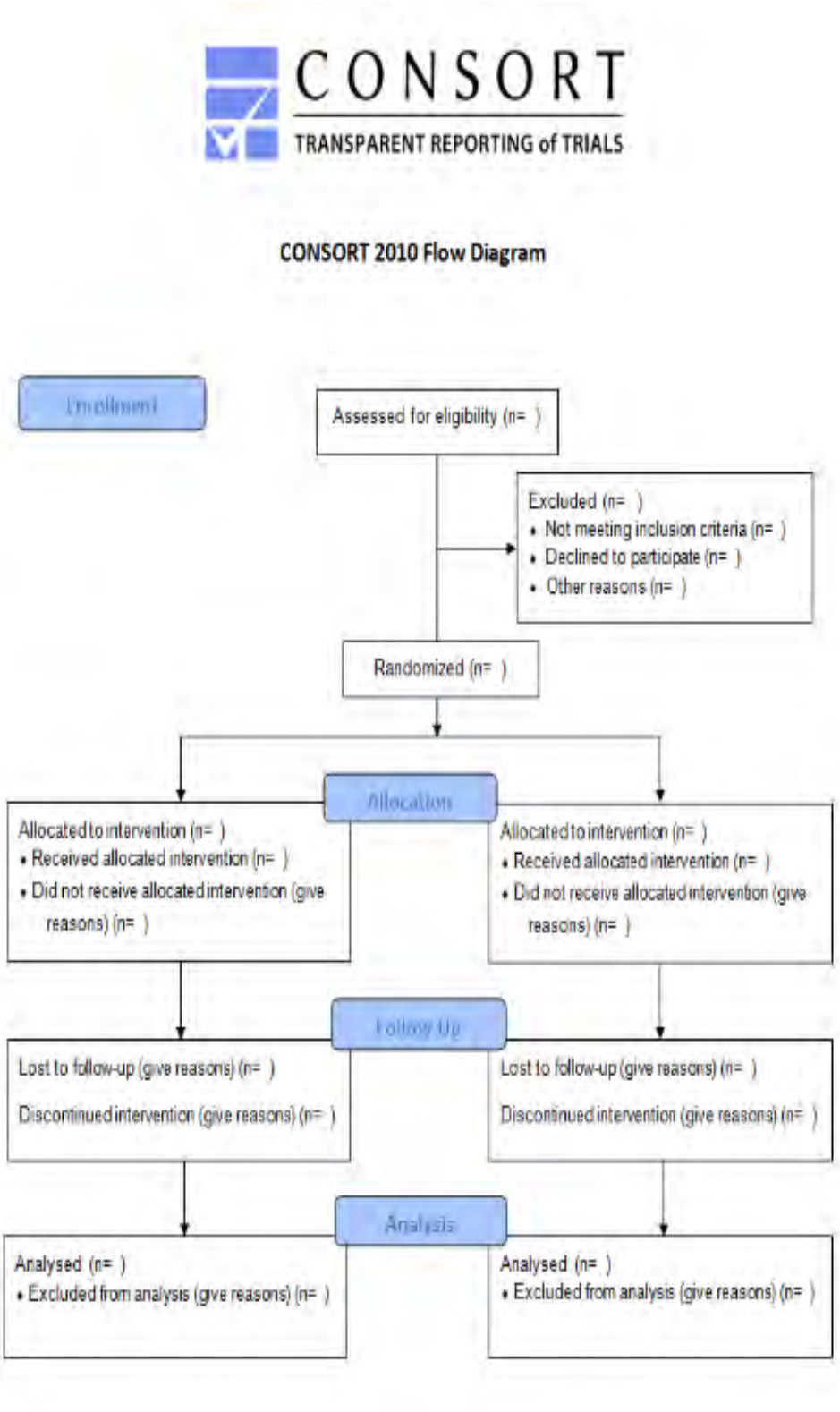


Figure 1. Flow diagram of the progress through the phases of a parallel randomised trial of two groups (enrolment, intervention allocation, follow-up, and data analysis)

Each item was subdivided as outlined in the CONSORT statement: 12 items were divided into a and b parts giving a total of 37 points scored per paper. Hence, based on CONSORT reporting items, we developed a 37-items data extraction sheet. We reviewed each article and determined whether the RCT paper reported on each of the 37 items of the revised CONSORT statement.

All items were investigated in terms of whether they were reported, not whether they were actually carried out during the trial. Each item was characterized as 'yes' if it was clearly and adequately reported in the trial or 'no' if it was partially reported, unclear, or not reported at all.

Each 'yes' answer received a score of 1 and each 'no' answer was scored as 0.

We conducted a descriptive statistical analysis of all evaluated articles. Data were analyzed using Microsoft Excel 2007.

In order to assess adherence to CONSORT checklist items, we calculated the number and proportion of trial articles that clearly and adequately reported each of the 37 CONSORT items (proportion of each item = the number of articles that reported the item /total articles-for example, if 3 of 5 RCTs reported item 8a on the checklist, that item would score an overall compliance score of 60%).

Although all items in the CONSORT checklist are considered important as to improve the quality of reports of RCTs, emphasis was placed on reporting of methodological items which are more specific to assess the methodological quality of RCTs, that is sample size, randomization (sequence generation, allocation concealment, implementation), blinding, performed statistical methods, description of baseline data, precision of estimated effect size and reporting of ITT analysis.

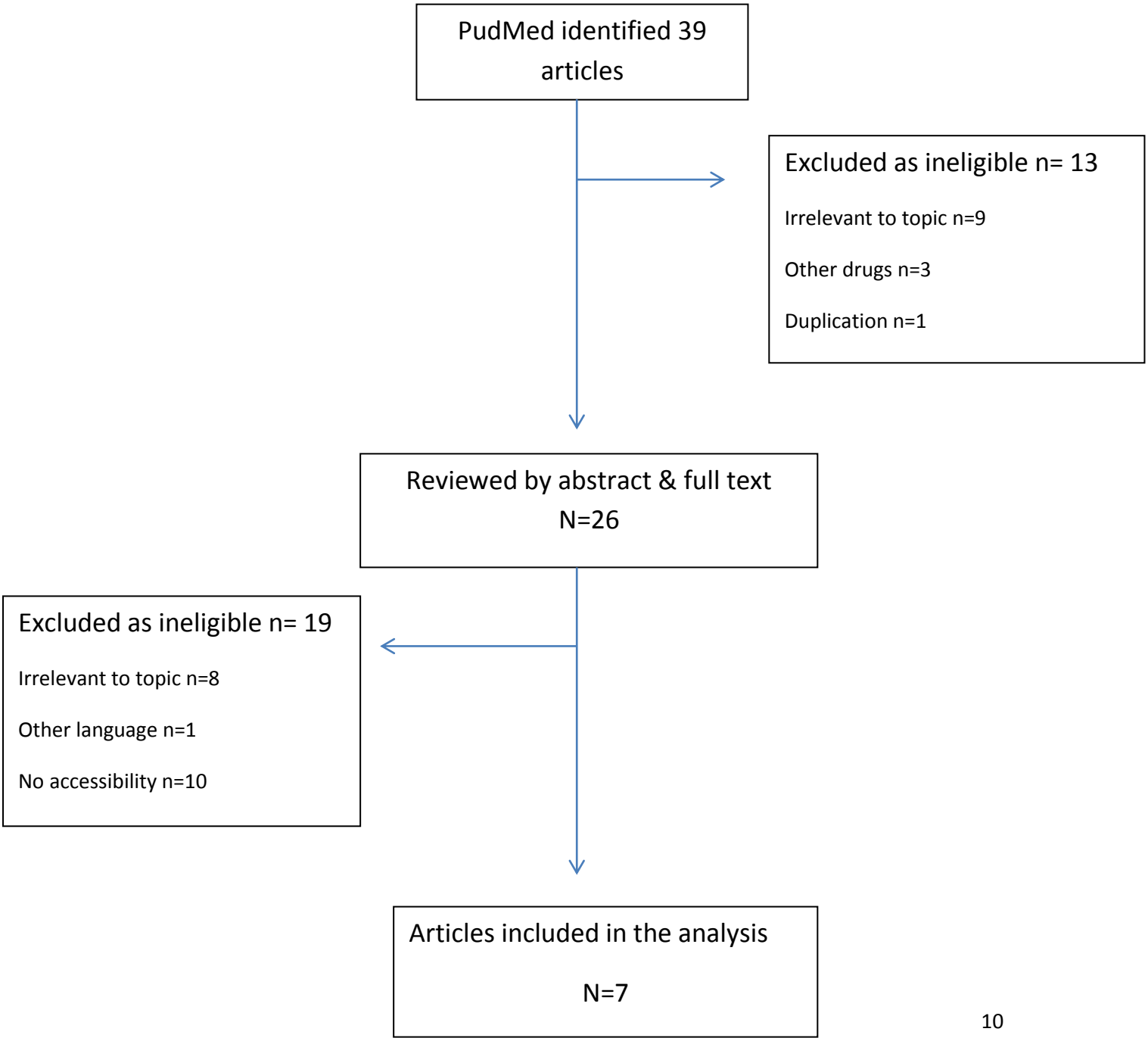
Explaining more specifically some methodological CONSORT criteria: i) randomization is the method used to generate the random allocation sequence, including details of any restriction (e.g. blocking, stratification) ii) allocation concealment is the method used to implement the random allocation sequence (e.g. numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned and iii) implementation of randomization answers the question of who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.

The total quality of reporting score (the CONSORT score) of each trial article was calculated as a proportion of the 'yes' rated applicable items on the CONSORT checklist (possible range 0-37 points) (CONSORT score of each article = the number of reported items/37 items-for example, a RCT reporting 20 of the 37 items on the checklist would score 54.1%), which was used to inform a global assessment of the quality of reporting.

D) RESULTS

Search results

The search in Pubmed yielded 39 potentially eligible articles that were screened for eligibility. 13 were excluded because they were not relevant or had a non medicinal intervention (behavioral treatment, exercise, herbal) or were not randomized trials. The 26 articles left reviewed by abstract and 9 excluded for the same reasons. 19 articles searched for full text from which 10 were not found due to accessibility reasons. 7 articles finally were evaluated and a list of them can be found at the Appendix.



Eligible trials

Finally, 7 RCTs were deemed eligible to be included in the present study. A full list of these RCTs is provided in the Appendix. Table 1 shows some basic characteristics of the included trials.

Table 1.

Characteristic	Categories	Number of RCTs
Journal of Publication	The new England journal	2
	Neurology	1
	Original communication	1
	Elsevier	2
	Journal of neuro-opthalmogy	1
Number of authors	≤ 10	5
	>10	2
Year of publication	2003	1
	2006	1
	2013	1
	2014	2
	2015	1
	2017	1
Type of control	Placebo	6
	Active control	3
Funding source	Pharmaceutical industries	6
	Others	1

Blinding	Blinded	5
	Open-label	2
RCT arms	2	5
	>2	2

Reporting quality results

The overall compliance for the 7 RCTs was 57,8% of applicable items.

Compliance figures for each item are summarized in Table 2.

CONSORT items have been variedly reported in the 69 RCTs. Compliance for each item ranges widely from 14% of trials to even 100% of trials (where the item is applicable). Items best reported (in >75% of RCTs) are:

- Item 1b (from the ‘’title and abstract’’ section), concerning the Structured summary of trial design, methods, results and conclusions, reported in 6 out of 7 RCTs
- Item 2a (from the ‘’background and objectives’’ section), concerning the Scientific background and explanation of rationale, reported in 6 out of 7 RCTs.
- Item 4a (from the ‘’participation’’ section) regarding to the eligibility criteria for participants, reported in 6 out of 7 RCTs.
- Item 5 (from the ‘’interventions’’ section) regarding to the interventions for each group with sufficient details to allow replication, including how and when they were actually administered, reported in 6 out of 7 RCTs.
- Item 12a (from the ‘’statistical methods’’ section) according to Statistical methods used to compare groups for primary and secondary outcomes, reported in 6 out of 7 RCTs.
- Item 13b (from the ‘’participant flow’’ section) concerning the losses and exclusions after randomization, together with reasons, for every group, reported in 6 out of 7 RCTs.
- Item 16 (from the ‘’number analyzed’’ section) regarding to the number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups, reported in 6 out of 7 RCTs.

- Item 17a (from the ‘’outcomes and estimation’’ section) concerning the results for each group, and the estimated effect size and its precision (such as 95% confidence interval) for each primary and secondary outcomes, reported in 6 out of 7 RCTs.

It should be noted that only item 13a concerning the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for primary outcome, for every group, respectively, reached a successful reporting proportion of 100% of the trials where it was applicable.

Table 2. Absolute number and proportion of RCTs reporting each of the CONSORT items

Data item		Number of RCTs reported	Proportion
1a		4	0.57
1b		6	0.85
2a	Background and objectives	6	0.85
2b		2	0.28
3a	Trial design	5	0.71
3b		3	0.42
4a	Participations	6	0.85
4b		4	0.57
5	Interventions	6	0.85
6a	Outcomes	5	0.71
6b		2	0.28
7a	Sample size	2	0.28
7b		2	0.28
8a	Sequence generation	5	0.71
8b		4	0.57
9	Allocation concealment Mechanism	1	0.14
10	Implementation	2	0.28
11a	Blinding	2	0.28
11b		2	0.28
12a	Statistical methods	6	0.85
12b		5	0.71
13a	Participant flow (a diagram is strongly recommended)	7	1
13b		6	0.85
14a	Recruitment	2	0.28
14b		3	0.42
15	Baseline data	5	0.71
16	Number analyzed	6	0.85
17a	Outcomes and estimation	6	0.85

17b		3	0.42
18	Ancillary analyses	3	0.42
19	Harms	4	0.57
20	Limitation	3	0.42
21	Generalizability	2	0.28
22	Interpretation	5	0.71
23	Registration	4	0.57
24	Protocol	4	0.57
25	Funding	4	0.57

On the contrary, successful reporting was particularly low (<25% of RCTs) for the item 9 regarding to the mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned. That item is reported in the 14% of the articles although it's an important methodological technique which should always be reported.

E) CONCLUSION

This thesis has evaluated the reporting quality of randomized controlled trials in the therapy of multiple sclerosis with natalizumab. The reports of 7 eligible trials were reviewed using the CONSORT 2010 statement as an assessment tool.

CONSORT, came about because of the need to provide readers with enough valid and meaningful information concerning the design, conduct, and analysis of RCTs, therefore it is expected that the CONSORT statement will ultimately lead to more comprehensive and complete reporting of RCTs. However our results summarized indicate that reports of RCTs involving patients with Multiple Sclerosis do not as yet conform to the CONSORT recommendations, neither have we found strong indications of improvement over time.

Many of the CONSORT checklist items are only reported in a minority of RCTs. Rather alarming is the fact that crucial methodological aspects for a RCT are underreported. Details about randomization, blinding, trial setup and timeframe are most often omitted. Information concerning harms, funding sources and protocol access are also frequently withheld. Summaries are also far from being written in a manner that best provides the reader with all the necessary information.

Nevertheless, some CONSORT items seem to be adequately reported in most of the trials: those referring to the scientific background, nature of interventions, eligibility criteria, statistical methods, baseline patient characteristics, interpretation of results.

However, these better reported items seem to represent more theoretical aspects of the trial.

This study has some limitations. First of all, the assessment of each report's compliance to the CONSORT items was undertaken by a single person, the author, thus rendering the procedure prone to subjectivity. The evaluation of each item was a rather complex procedure since no exact criteria exist as to what constitutes a positive or negative response. In order to address this problem, the CONSORT2010 Explanation and Elaborations document was thoroughly studied and each item was broken down into component elements derived from the document's elaboration on it. A positive response was accepted only when all of the component elements were met. Partial and ambiguous responses were counted as negative.

According to the above, the present study concluded that the reporting quality of the included RCTs for multiple sclerosis was suboptimal, even for key aspects of trial methodology. Due to the need for more effective treatments for multiple scleprosis, randomized controlled clinical trials will once again serve as the optimum way of verifying the safety and efficacy of new therapies. Better reports in terms of completeness and transparency, will help the scientific community evaluate their validity and reach safe decisions.

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10. Print version ISSN 0004-282X Arq. Neuro-Psiquiatr. vol.71 no.3 São Paulo Mar. 2013 http://dx.doi.org/10.1590/S0004-282X2013000300001 EDITORIAL Natalizumab and multiple sclerosis PhD, Neurologista, Chefe de Clínica das Enfermarias de Neurologia da, Santa Casa de Misericórdia do Rio de Janeiro 2Responsável pelo Ambulatório de Doenças Desmielinizantes da, Santa Casa da Misericórdia do Rio de Janeiro, Rio de Janeiro, RJ, Brazil

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APPENDIX

List of articles included in the study

1. MS disease activity in RESTORE, A randomized 24-week natalizumab treatment interruption study. Robert J. Fox, MD Bruce A.C. Cree, MD, PhD, MCR Jerome De Sèze, MD Ralf Gold, MD Hans-Peter Hartung, MD Douglas Jeffery, MD, PhD Ludwig Kappos, MD Michael Kaufman, MD Xavier Montalbán, MD, PhD Bianca Weinstock-Guttman, MD Britt Anderson, PhD Amy Natarajan, MS Barry Ticho, MD, PhD Petra Duda, MD, PhD
2. The new England journal of medicine, established in 1812 march 2, 2006 vol. 354 no. 9 A Randomized, Placebo-Controlled Trial of Natalizumab for Relapsing Multiple Sclerosis Chris H. Polman, M.D., Paul W. O'Connor, M.D., Eva Havrdova, M.D., Michael Hutchinson, M.D., Ludwig Kappos, M.D., David H. Miller, M.D., J. Theodore Phillips, M.D., Ph.D., Fred D. Lublin, M.D., Gavin Giovannoni, M.D., Andrzej Wajgt, M.D., Martin Toal, M.B., M.F.P.M., Frances Lynn, M.Sc., Michael A. Panzara, M.D., M.P.H., and Alfred W. Sandrock, M.D., Ph.D., for the AFFIRM Investigators*
3. Natalizumabreducesrelapseclinicalseverity and improves relapse recovery in MS$ Fred D.Lublina,n, GaryCutterb, GavinGiovannonic, AmyPaced, Nolan RCampbelld, ShibeshihBelachewd aIcahn
4. Clinical effects of natalizumab on multiple sclerosis appear early in treatment course Ludwig Kappos • Paul W. O'Connor • Christopher H. Polman • Patrick Vermersch • Heinz Wiendl • Amy Pace • Annie Zhang • Christophe Hotermans
5. A Controlled Trial of Natalizumab for Relapsing Multiple Sclerosis, David H. Miller, M.D., Omar A. Khan, M.D., William A. Sheremata, M.D., Lance D. Blumhardt, M.D., George P.A. Rice, M.D., Michele A. Libonati, M.S., Allison J. Willmer-Hulme, Ph.D., Catherine M. Dalton, M.B., Katherine A. Miszkiel, M.B., and Paul W. O'Connor, M.D., for the International Natalizumab Multiple Sclerosis Trial Group*
6. Efficacy, safety, and pharmacokinetics of natalizumab in Japanese multiple sclerosis patients: A double-blind, randomized controlled trial and openlabel pharmacokinetic study Takahiko Saidaa,, Jun-ichi Kirab, Shuji Kishidac, Takashi Yamamurad, Yukiko Sudoe, Kazutaka Ogiwarae, JT Tibunge, Nisha Lucasf, Meena Subramanyamf, On behalf of Natalizumab Trial Principal Investigators
7. Vision in a Phase 3 Trial of Natalizumab for Multiple Sclerosis: Relation to Disability and Quality of Life Salim Chahin, MD,corresponding author Laura J. Balcer, MD, MSCE, Deborah M. Miller, PHD, Annie Zhang, MD, MPH, and Steven L. Galetta, MD, FAAN